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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

**HED DOC. NO. 014469**

**DATE: February 8, 2001**

**MEMORANDUM**

**SUBJECT:** **Oxadiazon-** Report of the Hazard Identification Assessment Review Committee.

**FROM:** Nancy E. McCarroll, Toxicologist  
Toxicology Branch 1  
Health Effects Division (7509C)

**THROUGH:** Jess Rowland, Co-Chair  
and  
Elizabeth Doyle, Co-Chair  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)

**TO:** Seyed Tadayan, Chemist  
Chemistry and Exposure Branch I  
Health Effects Division (7509C)

**PC Code: 109001**

On December 7, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Oxadiazon with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to Oxadiazon was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: William Burnam, Pamela Hurley, David Nixon, Jess Rowland, Brenda Tarplee, and Yung Yang,

Member(s) in absentia: Elizabeth Doyle and Elizabeth Mendez

Data evaluation prepared by: Linnea Hansen/Nancy E. McCarroll, Toxicologist Branch 1

Also in attendance were: Ayaad Assad, Mike Ioannou, Alberto Protzel, Seyed Tadayan (HED)Jonathan Chen (AD), Veronique La Capra (SRRD)

Data Evaluation / Report Presentation: December 7, 2000

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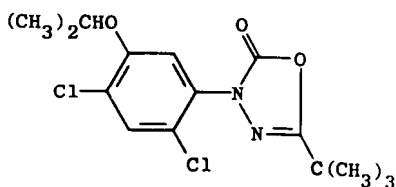
Linnea Hansen/Nancy E. McCarroll  
Toxicologists

## 1. INTRODUCTION

On December 7, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Oxadiazon with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to Oxadiazon was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

Oxadiazon, 5-tert-butyl-4-(2,4-dichloro-5-isopropoxyphenyl)-1,3,4-oxadiazol-2-one, is a selective pre-emergent and early post-emergence herbicide that is effective primarily for the control of annual grasses and broadleaf weeds in turf. Most of the usage is allocated to golf courses. The trade name for Oxadiazon in the U.S. is *Ronstar*. The mechanism of action is contact inhibition by affecting young shoots as they grow through the treated zone (pre-emergence) and complete coverage (post-emergence). Oxadiazon destroys cell membranes and inhibits photosynthesis, probably by generating oxidizing radicals in light. It is a powerful inhibitor of plant, yeast and mouse protoporphyrinogen oxidase, an enzyme critical in the biosynthesis of chlorophyll and heme (Matringe *et al.*, 1989). Oxadiazon has no food or feed uses. There are currently 16 tolerances in CFR 180.346; however, the registrant will delete these uses so that the tolerances can be revoked. The Registrant is now supporting use of Oxadiazon on golf courses, apartment/condo lawns, athletic fields, parks, playgrounds and cemeteries.

Oxadiazon has the following structure:



Empirical Formula: C<sub>15</sub> H<sub>18</sub> Cl<sub>2</sub> N<sub>2</sub> O<sub>3</sub>

Molecular Weight: 345.22

Melting Point: 88-90°C

Boiling Point: Not applicable (Oxadiazon is a solid)

Density: 20°C

Vapor Pressure at 20°C: <1 x 10<sup>-6</sup> mm Hg

Water Solubility: 0.7 mg/L at 20°C

Log Kow: 4.8

CAS Number: 19666-30-9

## 2. HAZARD IDENTIFICATION

### 2.1 Acute Reference Dose (RfD)

Not required since there are no food or feed or anticipated food or feed uses for this pesticide.

### 2.2 Chronic Reference Dose (RfD)

Not required since there are no food or feed or anticipated food or feed uses for this pesticide.

### 2.3 Occupational/Residential Exposure

#### 2.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Developmental Toxicity in Rats      Guideline #: 870.3700; 83-3a

MRID No.: 40470202

Executive Summary: In a developmental toxicity study (MRID 40470202), Oxadiazon technical (96.3%) was administered daily by gavage in 10 ml 1% aqueous methylcellulose vehicle/kg body weight from Gestation Days 6 through 15 to groups of 20 pregnant Sprague-Dawley rats per dose at 0, 3, 12 or 40 mg/kg/day. Pregnant females were examined daily for signs of toxicity and body weights were measured on Gestation Days 0, 3, 6, daily through Day 16 and on Days 18 and 20. Dams were sacrificed on Day 20 and uterine contents were examined.

Very little maternal toxicity was observed at any dose. Small but statistically significant decreases in body weight (-2% less than controls) and body weight gain (-10%) in the high-dose females at Days 16-20 were possibly due to resorptions of fetuses (decreased maternal body weights also observed at  $\geq 40$  mg/kg/day in the range-finding study). **The maternal toxicity LOAEL is 40 mg/kg/day, based on slightly decreased body weight/weight gain. The maternal toxicity NOAEL is 12 mg/kg/day.**

Treatment-related fetal toxicity at 40 mg/kg/day included: slightly, not statistically significantly increased fetal resorptions (0.7/dam vs. 0.4/dam, controls) and post-implantation loss (12.5% vs. 8.2%, controls), and significantly decreased body weight (4.5% less than controls). Developmental effects at 40 mg/kg/day were confined to increased incidence of incomplete ossification, primarily in skull and vertebral bones. No effects were seen at lower doses. No treatment-related malformations were observed at the doses tested. Fetal effects seen in this study are considered treatment-related based on the steep dose-response curve (for fetal loss and decreased fetal weight) between 20-60 mg/kg/day in the preliminary range-finding study. In the range-finding study, which tested at 10, 20, 40, 60 or 80 mg/kg/day (6 dams/dose group), no maternal or developmental toxicity was observed at 10 or 20

mg/kg/day. However, at 40 mg/kg/day, a mean fetal resorption rate of 40% (53-100% in 3/6 dams) was observed, increasing to 80-90% at 60 and 80 mg/kg/day. Weights of surviving fetuses were decreased. Decreased maternal weights were also observed at  $\geq 40$  mg/kg/day and were usually correlated with the increased litter resorption. Therefore, the effects seen at 40 mg/kg/day **in the main study** are considered a threshold response for Oxadiazon under the conditions of the main study. **The developmental toxicity LOAEL is 40 mg/kg/day, based on increased fetal resorptions/postimplantation loss, decreased fetal weight and increased incidence of incomplete ossification. The developmental toxicity NOAEL is 12 mg/kg/day.**

This study is classified **Acceptable/guideline**; it satisfies the guideline requirement for a developmental toxicity study (83-3a) in the rat.

Dose and Endpoint for Risk Assessment: NOAEL for maternal effects = 12 mg/kg/day. LOAEL = 40 mg/kg/day based on slight decrease in body weight/body weight gain at Days 16-20.

Comments about Study/Endpoint/Uncertainty Factor(s): This dose and endpoint were considered appropriate because the critical effect (body weight decrements) occurred during the treatment period (Gestation Days 16-20) which encompasses the exposure period of concern (1-7 days) and is appropriate for the population of concern (infants and children).

### **2.3.2 Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure**

Study Selected: Developmental Toxicity in Rats      Guideline #: 870.3700; 83-3a

MRID No.: 40470202

Executive Summary: See Short-term (1-7 Days) Incidental Oral Exposure

Dose and Endpoint for Risk Assessment: NOAEL for maternal effects = 12 mg/kg/day. LOAEL = 40 mg/kg/day based on slight decrease in body weight/body weight gain at Days 16-20.

Comments about Study/Endpoint: The dose and endpoint were considered appropriate because the NOAEL in the 90-day studies were higher than the NOAEL of this study. The NOAEL from the developmental study was selected because the lower maternal NOAEL may reflect greater sensitivity of the pregnant rat.

### **2.3.3 Dermal Absorption**

Dermal Absorption Factor: 9% from the dermal penetration study (10-hour reading)

MRID No.: 44588101

Executive Summary: In a dermal penetration study (MRID 44588101), <sup>14</sup>C-Oxadiazon (Lot No. GXR 396A--99.6% radiochemical purity, mixed with unlabeled Oxadiazon technical, 96% a.i.) in 1% aqueous carboxymethyl cellulose was administered dermally to groups of 24 male Sprague Dawley rats/dose at 5.45, 39.2 or 523  $\mu\text{g}/\text{cm}^2$  for exposure durations of 0.5, 1, 2, 4, 10 or 24 hours per dose (4 rats/exposure time). Urine and feces were collected; skin was excised and blood, residual urine and carcasses were collected and analyzed. Recovery of radioactivity ranged from 83.2% to 106% of administered dose.

The quantity of Oxadiazon in washed skin during the exposure phase ranged from 0.06-0.38, 0.59-3.31 or 2.88-15.32  $\mu\text{g}/\text{cm}^2$  at the low, mid or high dose, respectively. As a percentage of the administered dose, these were equivalent to 1.09%-6.89%, 1.50%-8.45% or 0.55%-2.93% (low to high dose, respectively). In general, the amount of absorbed test material was not detectable during the first 2 hours of exposure. Absorption ( $\mu\text{g}/\text{cm}^2$ ) was low throughout exposure and ranged from 0.06-0.6, 0.05-2.00 or 0.05-2.62  $\mu\text{g}/\text{cm}^2$  (low to high dose, respectively) at 4 to 24 hours; as a percent of the administered dose, these were equivalent to 1.11%-11.0%, 0.39%-5.11% or 0.01%-0.50%, respectively. The percent of test material on/or bound to the skin and the percent absorbed at 10 hours was 6.05% and 2.65% (5.45  $\mu\text{g}/\text{cm}^2$ ), 4.71% and 0.63% (39.2  $\mu\text{g}/\text{cm}^2$ ), and 1.03% and 0.05% (523  $\mu\text{g}/\text{cm}^2$ ), respectively. Since the percent of dose absorbed decreased with increasing dose and the quantity absorbed was essentially the same, the results indicate that absorption but not dermal uptake was saturated at 39.2 and 523  $\mu\text{g}/\text{cm}^2$ . Consequently, the percent bound to the skin and the percent absorbed in a 10-hour period is 6.05 and 2.65 %, respectively. For the purposes of risk assessment, the sum of both is 8.70%.

This study is classified **Acceptable/guideline**; it satisfies the guideline requirement for a dermal penetration study (85-3) in the rat.

Comments about Dermal Absorption: None

### **2.3.4 Short-Term Dermal (1-7 days) Exposure**

Study Selected: Developmental Toxicity in Rats      Guideline #: 870.3700; 83-3a

MRID No.: 40470202

Executive Summary: See Short-term (1-7 Days) Incidental Oral Exposure

Dose and Endpoint for Risk Assessment: NOAEL for developmental effects = 12 mg/kg/day. LOAEL = 40 mg/kg/day based on increased fetal resorptions/postimplantation loss, decreased fetal weight and increased incidence of incomplete ossification.

Comments about Study/Endpoint: A dermal study was submitted in which no systemic effects were seen up to the limit dose. However, since dermal studies do not evaluate developmental effects and there is a concern for increased susceptibility of the fetus to the test compound,

the Committee decided that the rat developmental study was more appropriate to set the dermal endpoint in conjunction with a dermal absorption factor.

### **2.3.5 Intermediate-Term Dermal (7 Days to Several Months) Exposure**

Study Selected: Developmental Toxicity in Rats      Guideline #: 870.3700; 83-3a

MRID No.: 40470202

Executive Summary: See Short-term Incidental **Oral** Exposure

Dose and Endpoint for Risk Assessment: See Short-term Incidental **Dermal** Exposure

Comments about Study/Endpoint: See Comments for Short-Term **Dermal** Study/Endpoint.

### **2.3.6 Long-Term Dermal (Several Months to Life-Time) Exposure**

Studies Selected: Combined Chronic Feeding/Oncogenicity-Rat      Guideline 870.4300/  
[83-5]

MRID Nos: (1) 40993401  
(2) 00149003/00157780

Executive Summary: In a chronic/oncogenicity toxicity study (MRID No. 40993401), Oxadiazon (95.9%) was administered to SPF Wistar rats (80/sex/dose) in the diet at dose levels of 0, 3, 10, 100 or 1000 ppm (equivalent to 0, 0.106, 0.36, 3.5 or 39 mg/kg/day for males or 0, 0.131, 0.44, 4.2 or 44 mg/kg/day for females) for 104 weeks. Clinical signs were monitored daily. Body weights were determined weekly for the first 26 weeks and biweekly, thereafter; food consumption was determined weekly for 20 rats/group. Groups of 8 rats/sex/group were sacrificed at weeks 26, 52 and 78 and 10 animals/sex/group at 104 weeks were subjected to hematology, biochemistry and urinalysis examinations. All 80 rats/sex/dose were reportedly examined for histopathology.

Dose selection was based on a preliminary 4-week range finding study with 10, 100, 1000 or 3000 ppm. At 1000 and 3000 ppm, signs of toxicity included: anemia (males--both groups; females--3000 ppm, only), effects on biochemical parameters associated with hepato-renal disorders (increased GOT, GPT, ALP, BUN, total cholesterol and/or urobilinogen), and liver and kidney weight changes accompanied by a dark color.

There were no adverse effects on mortality, clinical signs or food consumption. Treatment related effects included: decreased body weight gain for high-dose males generally throughout the study; statistically significant body weight losses (-8.9%) were reported for the 10 and 1000 ppm females only at study termination. Hematological parameters significantly affected were: decreased hematocrit and hemoglobin (high-dose males at week 26) and decreased mean corpuscular volume and mean corpuscular hemoglobin (high-dose males at weeks 26,

78 and 104). There were no consistent hematological effects in the females. The generalized changes in the blood elements of male rats are indicative of anemia which was most evident at week 26. Significantly affected clinical chemistry parameters included: increased LDH, ALP, GOT, GPT, total and direct bilirubin and total cholesterol for high-dose males at week 26; no toxicologically significant effects were seen in the females of any dose group. At 1000 ppm, males also showed increased urobilinogen at week 26. Increased liver weights were seen in high-dose males and females throughout the study and statistically significant increases in kidneys (both sexes) and testis (males) were also consistently seen at 1000 ppm. Non-neoplastic pathology in the liver at 1000 ppm included: ↑centrilobular hepatocellular swelling (♂ and ♀); ↑acidophilic foci of cellular alteration (♂); brown pigmentation in the liver (♂ and ♀); and bile duct proliferation (♂). At 100 ppm, ↑centrilobular hepatocellular swelling was also seen in the males. Brown pigmentation in the proximal tubular cells and in cortical interstitial tissue (♂ and ♀); and chronic nephropathy (♀) were also recorded for the kidneys of high-dose rats.

**The LOAEL is 100 ppm (3.5 mg/kg/day) based on centrilobular swelling in the male rat livers; the NOAEL is 10 ppm (0.36 mg/kg/day).**

**Neoplastic findings were: increased incidence of liver adenomas in males at 100 (p<0.05) and 1000 ppm (p<0.010); liver carcinomas were also increased at 1000 ppm in both sexes but not significantly.**

The pathology report for this chronic/carcinogenicity study in the rat was considered incomplete; thus, the overall study was listed as Supplementary. At this time, no additional information is being requested because the results are consistent with an acceptable rat chronic/carcinogenicity study (MRID No. 0014003/00157780) that satisfies the guideline requirement. Similarly, the presence of liver neoplasms confirms the evidence of a carcinogenic effect seen in MRID No. 0014003/00157780. Using the more recent terminology, the study is now listed as **Unacceptable/guideline** (MRID No. 40993401).

Executive Summary: In a chronic/carcinogenicity toxicity study (00149003/00157780), Oxadiazon (99.9%) was administered to Fischer 344 rats (76/sex/dose) in the diet at dose levels of 0, 10, 100, 1000 or 3000 ppm (mean consumption per group: equivalent to 0, 0.5, 4.8, 50.9 or 163.1 mg/kg/day for males or 0, 0.6, 5.9, 60.9 or 192.7 mg/kg/day for females) for 24 months. Parameters examined included: (1) twice daily observations, (2) weekly body weights and food consumption, (3) ophthalmic examinations (all animals at pretest and 10 rats/group at 6, 12 and 24 months), (4) standard hematology, clinical chemistry and urinalysis (10 rats/group at 6, 12 and 24 months), and (5) gross necropsy, organ weights and histology (10 rats/group at 6 and 12 months and all survivors at 24 months).

There were no effects on mortality. At 1000 and 3000 ppm, clinical signs included emaciation, anemia and brown colored urine; ophthalmic examinations revealed narrowing of the fundus vasculature (♂ at 1000 ppm and both sexes at 3000 ppm). Significant decreases (p<0.05-0.001) in body weight gain were apparent in rats of both sexes receiving 1000 or 3000 ppm and significant decreases in food consumption were recorded for both sexes

starting at week 3 (males) and week 6 (females). Consistent hematological findings indicative of anemia at 3000 ppm (both sexes) were: significantly decreases erythrocyte counts, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Anemia was also present in males at 1000 ppm and appeared to be less severe in females. Adverse effects on urinalysis parameters were confined to the two highest dose groups (both sexes) and included: urine color, strongly positive bilirubin and urobilinogen. Significantly affected clinical chemistry parameters included: reduced glucose levels ( $\sigma \geq 1000$  ppm at 6 and 12 months;  $\text{♀}$  3000 ppm at 6 months); increased total protein (consistent effect only in the  $\text{♀}$  at  $\geq 100$  ppm and generally at all sampling intervals); increased total cholesterol ( $\sigma$  at 1000 ppm and both sexes at 3000 ppm) and increased bilirubin ( $\sigma \geq 1000$  ppm at 6 and 12 months;  $\text{♀}$  3000 ppm at 6 months). In addition, significant increases in GOT, GPT, AP and BUN generally correlated well with liver morphological changes at  $\geq 1000$  ppm ( $\sigma$ ). Similarly, increased absolute and relative liver and kidney weights at  $\geq 1000$  ppm (both sexes) correlated well with liver and kidney histopathology effects. At termination, Oxadiazon also induced increased absolute and relative liver weights at 100 ppm ( $\text{♀}$ ). Non-neoplastic pathology included: hepatocyte changes consisting of progressive alterations from hypertrophy through fatty changes to necrosis were noted in males receiving 1000 and 3000 ppm and females receiving 3000 ppm. Other non-neoplastic changes noted in both sexes were: pigmented nephrosis and fat replacement in the pancreas at 1000 ppm and basophilic changes in the adrenal glands at 3000 ppm.

**The LOAEL is 100 ppm (5 mg/kg/day) based on increased absolute liver weights in males and females and increased total serum protein in females. The NOAEL is 10 ppm (0.5 mg/kg/day).**

**Neoplastic findings were: increased incidences of benign and malignant liver tumors in males at 1000 and 3000 ppm after prolonged exposure to hepatotoxic doses. In addition, there was no decrease in latency for liver neoplasia.**

This chronic/carcinogenicity study in the rat is **Acceptable (Guideline)** and satisfies the guideline requirement for a combined chronic/carcinogenicity study (83-5) in the rat (MRID Nos. 00149003 [main study]/MRID 00157780 [additional data]).

Dose and Endpoint for Risk Assessment: NOAEL = 0.36 mg/kg/day. LOAEL = 3.5 mg/kg/day based on centrilobular swelling in the male rat livers.

Comments about Study/Endpoint: The pathology report for the selected chronic/carcinogenicity study in the rat was considered incomplete and the overall study was listed as Supplementary (**Unacceptable**). However, no additional information is being requested because the results are consistent with an acceptable rat chronic/carcinogenicity study (MRID No. 0014003/00157780). This study was chosen by IRIS in 1986 to set the chronic RfD for Oxadiazon. The NOAEL and LOAEL for this study was 0.5 and 5 mg/kg/day, respectively, based on increased liver weights in both sexes and increased serum protein in females. Thus, the findings from MRID No. 0014003/00157780 support the selected NOAEL and LOAEL. In addition, liver neoplasms in males were present in both

studies and confirms the evidence of a carcinogenic effect. While both studies were in good agreement, the study selected for this endpoint (MRID No. 40993401) is considered **Unacceptable**. **The HIARC concluded, however, that in combination with the Acceptable study used by IRIS and within the context of the entire database, MRID No. 40993401 was Acceptable for endpoint selection. Additionally, since an oral NOAEL was selected for this risk assessment, the dermal absorption factor should be used for route-to-route extrapolation.**

### **2.3.7 Inhalation Exposure (All Durations)**

#### **Studies Selected:**

**Short- and Intermediate-Term:** Developmental Oral Study in Rats (MRID No. 40470202)  
NOAEL = 12 mg/kg/day

**Executive Summary:** See Short-term Incidental Oral Exposure

**Long-Term:** Combined Chronic Feeding /Oncogenicity in Rats (MRID Nos. 40993401 and 0014003/00157780)  
NOAEL = 0.36 mg/kg/day

**Executive Summaries:** See Long-Term Dermal (Several Months to Life-Time) Exposure

**Comments about Study/Endpoint:** With the exception of an acute inhalation study (MRID No. 41866503) in which Oxadiazon was placed in Category III ( $LC_{50} > 1.94$  mg/L), no other inhalation studies are available for this risk assessment. **Consequently, the HIARC recommended the submission of a 28- day inhalation toxicity study. Until that time, the HIARC recommended using route-to-route extrapolation since the doses identified for the short and intermediate term and for the long term inhalation exposures are from oral studies. The following route-to-route extrapolation steps should be followed:**

Step 1: Convert the inhalation exposure ( $\mu\text{g/lb a.i.}$ ) using a 100% inhalation absorption rate (default value), application rate and acres treated to an **oral equivalent dose** (mg/kg/day).

Step 2: Convert the dermal exposure (mg/kg/day) using 9% as the dermal absorption rate, application rate and acres treated to an **oral equivalent dose** (mg/kg/day). This dose should be combined with the converted oral dose in Step 1.

Step 3: To calculate the MOE's, the combined dose from Step II should be compared to the oral NOAEL of 12 mg/kg/day for the Short-and Intermediate-term exposure scenarios and to the oral NOAEL of 0.36 mg/kg/day for the Long- term exposure scenarios.

### **2.3.8 Margins of Exposure for Occupational/Residential Risk Assessments**

There are no food or feed uses of Oxadiazon. For nonoccupational and occupational exposure risk assessments, a MOE of 100 is required for dermal and inhalation exposures. The Registrant is now supporting use of Oxadiazon on golf courses, apartment/condo lawns, athletic fields, parks, playgrounds and cemeteries. Many of these sites, including golf courses are considered a residential use with respect to the post-application risk assessment.

### **2.4 Recommendation for Aggregate Exposure Risk Assessments**

Since there are no food uses, aggregate exposure will be limited to combining the dermal and inhalation exposure components since oral equivalents were selected.

## **3 CLASSIFICATION OF CARCINOGENIC POTENTIAL**

### **3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats**      Guideline #: 870.4300/ [83-5]

MRID No.: 00149003/00157780

Executive Summary: In a chronic/carcinogenicity toxicity study (00149003/00157780), Oxadiazon (99.9%) was administered to Fischer 344 rats (76/sex/dose) in the diet at dose levels of 0, 10, 100, 1000 or 3000 ppm (mean consumption per group: equivalent to 0, 0.5, 4.8, 50.9 or 163.1 mg/kg/day for males or 0, 0.6, 5.9, 60.9 or 192.7 mg/kg/day for females) for 24 months. Parameters examined included: (1) twice daily observations, (2) weekly body weights and food consumption, (3) ophthalmic examinations (all animals at pretest and 10 rats/group at 6, 12 and 24 months), (4) standard hematology, clinical chemistry and urinalysis (10 rats/group at 6, 12 and 24 months), and (5) gross necropsy, organ weights and histology (10 rats/group at 6 and 12 months and all survivors at 24 months).

There were no effects on mortality. At 1000 and 3000 ppm, clinical signs included emaciation, anemia and brown colored urine; ophthalmic examinations revealed narrowing of the fundus vasculature (♂ at 1000 ppm and both sexes at 3000 ppm). Significant decreases ( $p < 0.05$ - $0.001$ ) in body weight gain were apparent in rats of both sexes receiving 1000 or 3000 ppm and significant decreases in food consumption were recorded for both sexes starting at week 3 (males) and week 6 (females). Consistent hematological findings indicative of anemia at 3000 ppm (both sexes) were: significantly decreases erythrocyte counts, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Anemia was also present in males at 1000 ppm and appeared to be less severe in females. Adverse effects on urinalysis parameters were confined to the two highest dose groups (both sexes) and included: urine color, strongly positive bilirubin and urobilinogen. Significantly affected clinical chemistry parameters included: reduced glucose levels (♂  $\geq 1000$  ppm at 6 and 12 months; ♀ 3000 ppm at 6 months); increased total protein (consistent effect only in the ♀ at  $\geq 100$  ppm and generally at all

sampling intervals); increased total cholesterol (♂ at 1000 ppm and both sexes at 3000 ppm) and increased bilirubin (♂ ≥1000 ppm at 6 and 12 months; ♀ 3000 ppm at 6 months). In addition, significant increases in GOT, GPT, AP and BUN generally correlated well with liver morphological changes at ≥1000 ppm (♂). Similarly, increased absolute and relative liver and kidney weights at ≥1000 ppm (both sexes) correlated well with liver and kidney histopathology effects. At termination, Oxadiazon also induced increased absolute and relative liver weights at 100 ppm (♀). Non-neoplastic pathology included: hepatocyte changes consisting of progressive alterations from hypertrophy through fatty changes to necrosis were noted in males receiving 1000 and 3000 ppm and females receiving 3000 ppm. Other non-neoplastic changes noted in both sexes were: pigmented nephrosis and fat replacement in the pancreas at 1000 ppm and basophilic changes in the adrenal glands at 3000 ppm.

**The LOAEL is 100 ppm (5 mg/kg/day) based on increased absolute liver weights in males and females and increased total serum protein in females. The NOAEL is 10 ppm (0.5 mg/kg/day).**

Discussion of Tumor Data: Neoplastic findings were: increased incidences of benign and malignant liver tumors in males at 1000 and 3000 ppm after prolonged exposure to hepatotoxic doses. In addition, there was no decrease in latency for liver neoplasia.

Adequacy of the Dose Levels Tested: Dosing was considered adequate in males and in females and the data support a presumption that the maximum tolerated dose (MTD) lies between 100 and 1000 ppm.

This chronic/carcinogenicity study in the rat is **Acceptable (Guideline)** and satisfies the guideline requirement for a combined chronic/carcinogenicity study (83-5) in the rat (MRID Nos. 00149003 [main study]/MRID 00157780 [additional data]).

MRID No.: 40993401

Executive Summary: In a chronic/oncogenicity toxicity study (MRID No. 40993401), Oxadiazon (95.9%) was administered to SPF Wistar rats (80/sex/dose) in the diet at dose levels of 0, 3, 10, 100 or 1000 ppm (equivalent to 0, 0.106, 0.36, 3.5 or 39 mg/kg/day for males or 0, 0.131, 0.44, 4.2 or 44 mg/kg/day for females) for 104 weeks. Clinical signs were monitored daily. Body weights were determined weekly for the first 26 weeks and biweekly, thereafter; food consumption was determined weekly for 20 rats/group. Groups of 8 rats/sex/group were sacrificed at weeks 26, 52 and 78 and 10 animals/sex/group at 104 weeks were subjected to hematology, biochemistry and urinalysis examinations. All 80 rats/sex/dose were reportedly examined for histopathology.

Dose selection was based on a preliminary 4-week range finding study with 10, 100, 1000 or 3000 ppm. At 1000 and 3000 ppm, signs of toxicity included: anemia (males--both groups; females--3000 ppm, only), effects on biochemical parameters associated with hepato-renal disorders (increased GOT, GPT, ALP, BUN, total cholesterol and/or urobilinogen), and liver and kidney weight changes accompanied by a dark color.

There were no adverse effects on mortality, clinical signs or food consumption. Treatment related effects included: decreased body weight gain for high-dose males generally throughout the study; statistically significant body weight losses (-8.9%) were reported for the 10- and 1000 ppm females only at study termination. Hematological parameters significantly affected were: decreased hematocrit and hemoglobin (high-dose males at week 26) and decreased mean corpuscular volume and mean corpuscular hemoglobin (high-dose males at weeks 26, 78 and 104). There were no consistent hematological effects in the females. The generalized changes in the blood elements of male rats are indicative of anemia which was most evident at week 26. Significantly affected clinical chemistry parameters included: increased LDH, ALP, GOT, GPT, total and direct bilirubin and total cholesterol for high-dose males at week 26; no toxicologically significant effects were seen in the females of any dose group. At 1000 ppm, males also showed increased urobilinogen at week 26. Increased liver weights were seen in high-dose males and females throughout the study and statistically significant increases in kidneys (both sexes) and testis (males) were also consistently seen at 1000 ppm. Non-neoplastic pathology in the liver at 1000 ppm included: ↑centrilobular hepatocellular swelling (♂ and ♀); ↑acidophilic foci of cellular alteration (♂); brown pigmentation in the liver (♂ and ♀); and bile duct proliferation (♂). At 100 ppm, ↑centrilobular hepatocellular swelling was also seen in the males. Brown pigmentation in the proximal tubular cells and in cortical interstitial tissue (♂ and ♀); and chronic nephropathy (♀) were also recorded for the kidneys of high-dose rats.

**The LOAEL is 100 ppm (3.5 mg/kg/day) based on centrilobular swelling in the male rat livers; the NOAEL is 10 ppm (0.36 mg/kg/day).**

**Discussion of Tumor Data: Neoplastic findings were: increased incidence of liver adenomas in males at 100 (p<0.05) and 1000 ppm (p<0.010); liver carcinomas were also increased at 1000 ppm in both sexes but not significantly.**

**Adequacy of the Dose Levels Tested:** Dosing was considered adequate in males based on signs of transient anemia, ↑ serum enzyme activity, ↑ bilirubin and liver weight, ↓ body weight gain, and pathological changes in the liver (centrilobular hepatocellular swelling and foci of cellular alteration). Females were considered to be tested at a dose below the maximum tolerated dose (MTD). However, since the NOAEL and LOAEL were defined for males (0.36/3.5 mg/kg/day), the hypothetical values for females are expected to be higher. Hence, the NOAEL and LOAEL for males are considered to be protective for females.

The pathology report for this chronic/carcinogenicity study in the rat was considered incomplete; thus, the overall study was listed as Supplementary. At this time, no additional information is being requested because the results are consistent with an acceptable rat chronic/carcinogenicity study (MRID No. 0014003/00157780) that satisfies the guideline requirement. Similarly, the presence of liver neoplasms confirms the evidence of a carcinogenic effect seen in MRID No. 0014003/00157780. Using the more recent terminology, the study is now listed as **Unacceptable/guideline** (MRID No. 40993401).

### 3.2 Carcinogenicity Study in Mice [83-2]

Guideline #: 870.4200/

MRID No.: 00115733

Executive Summary: In a mouse oncogenicity study (MRID No. 00115733), Oxadiazon (tech., 99.3% a.i., Lot/Batch # BES 2253) was administered in the diet to CD-1 mice (70/sex/group) for up to 105 weeks at 0, 100, 300, 1000, or 2000 ppm (equivalent to 0/0, 12/14, 37/44, 122/143, or 254/296 mg/kg/day [M/F], respectively).

At 2000 ppm, significantly decreased survival (and a dose-related positive trend for decreased survival) were observed in males (at termination, 43%, 24%, 36%, 27% and 4%, control to high dose) and in females (at termination, 56%, 41%, 53%, 43% and 29%). During the first 26 weeks of treatment, 29/70 high-dose males died or were sacrificed *in extremis*. It was stated that these animals were generally pale, inactive, weak, hypothermic and exhibited tremor and piloerection. Thoracic serosanguineous fluid was observed in these males at gross necropsy (15/29 treated vs 6/70 total controls affected and 1 of 2 controls that died by week 26). At histological examination, the following were also observed (# of animals): hypercellular spleens (18); diffuse, necrotic myocarditis (20); periportal hepatocytic pallor (12); hepatic single cell necrosis (16); and pigmented Kupffer cells (8). An increase ( $p < 0.05$  or  $0.01$ ) in the total incidence of distended abdomen was observed at various intervals in all treated males (80-90% treated vs 60-61% controls). Pale eyes were observed in females (50-60% treated vs 31% controls). At 1000 and 2000 ppm, increased ( $p < 0.05$  or  $0.01$ ) incidence of pallor was observed (40-46% treated vs 21% controls) during the study. At 2000 ppm, body weights were reduced in males at week 104 ( $\downarrow 12\%$ , not analyzed statistically). Reductions ( $p < 0.05$  or  $0.01$ ) in mean body weight gain were observed in the males during weeks 1-13 ( $\downarrow 13\%$ ) and for weeks 0-104 ( $\downarrow 26\%$ ); during weeks 66-92, weight loss was greater at high dose than controls ( $-7$  g vs.  $-2$  g, respectively). Slight anemia, as indicated by decreased ( $p < 0.05$ ,  $0.01$ , or  $0.001$ ) hematocrit ( $\downarrow 5$ -30%), hemoglobin ( $\downarrow 6$ -28%), and erythrocyte count ( $\downarrow 12$ -32%), was observed in the 1000 ppm males and 2000 ppm males and females. Neutrophil count was slightly increased at 2000 ppm in males ( $\uparrow 83\%$ ) and females ( $\uparrow 117\%$ ) at termination, possibly reflecting a mild inflammatory response.

Increases ( $p < 0.05$ ,  $0.01$ , or  $0.001$ ) with respect to concurrent controls were observed in absolute and relative (to body weight) liver weights in all male treatment groups ( $\uparrow 45\%/52\%$ ,  $46\%/57\%$ ,  $107\%/120\%$  and  $86\%/120\%$ ) and in the 1000 and 2000 ppm female groups ( $\uparrow 48\%/53\%$  and  $103\%/102\%$ ). At gross necropsy, increased incidence of hepatic pale areas/foci and masses were observed in all male groups when excluding animals that died before week 27 (pale areas/foci 36%-59% treated vs 4% controls; masses 41%-47% treated vs 27% controls) and all female groups (pale areas/foci 11%-19% treated vs 7% controls; masses 10%-26% treated vs 3% controls). In addition, raised areas in the liver were observed in the 300, 1000, and 2000 ppm females (10-11% vs 1% control). Increases in large, eosinophilic hepatocytes were observed in all male and female groups without a clear dose-response (7-23 treated affected vs 0-3 controls,  $N = 70$ , all groups). Slight to moderate hepatic amyloidosis was increased in all male treatment groups (9-22 treated affected vs. 0

controls) and in high-dose females (12/70 treated vs 3/70 controls). Increased incidence of pigmented Kupffer cells (7/41 treated vs 0/70 controls) were observed in males that did not die by week 26. Food consumption, food efficiency, and water consumption (visually inspected, only) for both sexes at all doses were unaffected by treatment with Oxadiazon at any tested dose. **The systemic toxicity LOAEL is  $\leq 100$  ppm for males and females (equivalent to 12/14 mg/kg/day [M/F]) based on clinical signs, gross and microscopic liver lesions in both sexes, and increased liver weights in males. The systemic toxicity NOAEL is  $<100$  ppm.**

Discussion of Tumor Data: **Under the conditions of this study, there was an increased incidence of hepatocellular neoplasms in males and females.** Incidences of hepatocellular adenomas were increased ( $p < 0.05$ , 0.01, or 0.001) in all groups of treated males (27.9%, 51.4%, 68.6%, 56.5% and 53.7%-68.6%, control to high dose) and females (4.4%, 18.8%, 25.7%, 32.9% and 41.2%) treatment groups. These were outside of historical control ranges of males (0-12%) in all groups, including controls, and of females (0-14%) for all treated groups. The incidences of adenocarcinomas were increased ( $p < 0.05$  or not significant) in all male treatment groups (7.4%, 20.0%, 24.3%, 24.6% and 24.4%, control to high dose) and in the 1000 and 2000 ppm female groups (12.9% and 10.3% vs 1.5%, controls). The incidences were outside of historical control ranges for males (0-8%) in all treatment groups and females (0-6%) at  $\geq 1000$  ppm. The incidences of combined adenomas and adenocarcinomas were increased ( $p < 0.05$ , 0.01, or 0.001) in all male (29.4%, 57.1%, 74.3%, 63.8% and 68.3%) and female (5.9%, 18.8%, 27.1%, 38.6% and 47.1%) treatment groups (no historical controls provided for combined neoplasms).

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on the finding of liver toxicity at all doses.

The submitted study is classified as **Acceptable/guideline (§83-2b)** and satisfies the guideline requirements for a carcinogenicity study in mice (MRID No. 00115733).

MRID No.: 00044322

Executive Summary: In an oral mouse oncogenicity study (MRID 00044322), Oxadiazon (95.5% a.i., Lot/Batch # MAG 405) was administered in the diet to CD-1 mice (60/sex/group) for up to 104 weeks at 0, 300, 1000 or 2000 ppm (equivalent to 0/0, 48/62, 153/201, and 319/417 mg/kg/day [M/F], respectively. Actual daily dosage may have been slightly lower, based on the analytical diet concentrations). At study initiation, high-dose animals received 3000 ppm diets. Due to high mortality, the compound was removed from the high-dose diet for weeks 2 and 3, then dosing was re-initiated at 2000 ppm. Animals that died during weeks 1-5 (10 males, 3 females) were replaced with parallel treated animals or control replacement animals that had not previously received the test article. No interim sacrifice was performed.

Toxicity to the liver was observed at all doses. At 300 ppm, statistically significantly increased serum alkaline phosphatase (+60% above controls) and ALT or SGPT (+270%) in

females, along with a non-significant increase in AST or SGOT (+76%, females) and ALT (+75%, males), and statistically significant increases in abs/rel liver weights in both males (+26%/+34%) and females (+50%/+60%) were observed. These parameters usually showed dose-dependent increases at  $\geq 1000$  ppm. Grossly visible liver masses (combined males/females 38% vs. 9%, controls) and liver microscopic lesions (bile duct proliferation, pigmented macrophages, diffuse hepatocellular hyperplasia, nodular hyperplasia, nodular hypertrophy and centrilobular hypertrophy) were increased at  $\geq 300$  ppm in both sexes. Some of these lesions did not show a dose-response, but were still considered treatment-related. At 1000 ppm, significantly increased serum alkaline phosphatase (+620%), AST (+104%), ALT (+218%) and cholesterol (+82%) were observed in males, and possibly lenticular degeneration in the eyes of males (10% vs. 0, controls). At 2000 ppm, most of these parameters showed additional increases and significantly increased cholesterol in females (+81%), increased lenticular degeneration in the eyes of males (25% vs. 0%, controls) and liver focal necrosis in males (54% vs. 35%, controls) and females (41% vs. 25%, controls) were also observed. A 16% decrease in hematocrit in males was considered of equivocal biological significance. Survival (after lowering of high dose to 2000 ppm), clinical signs, body weights, food consumption/efficiency and urine occult blood in both sexes were unaffected at all dose levels. **The systemic toxicity LOAEL is  $\leq 300$  ppm (approximately 48/62 [M/F] mg/kg/day) based on increased liver effects in both sexes. The systemic toxicity NOAEL is  $< 300$  ppm.**

Discussion of Tumor Data: **Under the conditions of this study, there was evidence of an increased incidence of hepatocellular carcinoma in both sexes.** The increase was significant ( $p < 0.01$ ) in both sexes at 1000 (males - 24/60 or 40% vs 5/60 or 8.3%, controls; females - 12/61 or 19.7% vs 1/60 or 1.7%, controls) and 2000 ppm (27/69 or 39.1%, males and 13/63 or 20.6%, females). The incidence at 300 ppm in both males (7/60 or 11.7%) and females (4/60 or 6.7%) was not significant.

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on the finding of liver toxicity at all doses.

The submitted study is classified as **Unacceptable/guideline (§83-2b)**. Although several study deficiencies were identified, the additional information is not being requested at this time because the results are consistent with an acceptable mouse carcinogenicity study (MRID No. 00149003/00157780) that satisfies the guideline requirement. In the current study, the following were noted: (1) the summary tables of the gross pathology findings (Tables 9 and 10) were illegible in the only study copy available for review and (2) it was unclear from the study report what system of classification of liver proliferative and neoplastic microscopic lesions were used in this study compared to current conventions of classification. Although hepatocellular carcinomas were increased in treated animals, no adenomas were reported, which are generally observed as part of the tumor progression (MRID No. 00044322).

MRID No.: 40993301

Executive Summary: In a chronic/oncogenicity toxicity study (MRID No. 40993301), Oxadiazon (95.9%) was administered to 80 ICR-JCL mice (80/sex/dose) in the diet at 0, 3, 10, 100 or 1000 ppm (equivalent to 0, 0.315, 1.09, 10.6 or 113 mg/kg/day for males or 0, 0.278, 0.92, 9.3 or 99 mg/kg/day for females) for 98-99 weeks (the study was scheduled to run for 104 weeks but due to deaths, it was terminated at 98-99 weeks). Clinical signs were monitored daily. Body weights were determined weekly for the first 26 weeks and biweekly, thereafter; food consumption was determined twice weekly for 8 cages (4 mice/cage). Groups of 9-10 mice/sex/group were sacrificed at weeks 52 and 98/99 were subjected to hematology, biochemistry, urinalysis and pathology analysis.

Dose selection was based on a preliminary 4-week range finding study with 0, 10, 100, 1000 or 3000 ppm. Liver weights were increased in males at 100, 1000 and 3000 ppm and in females at 1000 and 3000 ppm. Signs of anemia were reported for both sexes at  $\geq 1000$  ppm. Elevated GOT and GPT (indicative of hepatic toxicity) was also evident at 1000 and 3000 ppm ( $\sigma$ ) and 3000 ppm ( $\varphi$ ).

There were no consistent adverse effects on mortality, clinical signs, body weight or food consumption. Hematological parameters significantly affected in male mice were: decreased hematocrit, hemoglobin and erythrocyte counts (all exposure groups at week 52 but not at week 98); and decreased mean corpuscular volume and mean corpuscular hemoglobin (high-dose males at weeks 52 and 98). In females, significantly decreased hemoglobin, mean corpuscular volume and decreased mean corpuscular hemoglobin were observed at 1000 ppm after 52 weeks of treatment. The generalized changes in these blood elements are indicative of anemia which was most evident in the males at week 52. Significantly affected clinical chemistry parameters at 1000 ppm included: increased GLP, GOT, ALP and BUN ( $\sigma$  and  $\varphi$ ) and at 100 ppm were: increased GLP and GOT( $\sigma$ ). High-dose males also had brownish colored urine at week 52. Significantly increased liver weights (absolute/relative) were seen in high-dose males at weeks 52 and 98 and in high-dose females at week 98. Significant increases in absolute and relative adrenal ( $\sigma$  week 98) and kidney ( $\varphi$  week 98) weights were also seen at 1000 ppm. Non-neoplastic pathology at 1000 ppm included:  $\uparrow$  centrilobular hepatocellular swelling ( $\varphi$ );  $\uparrow$  diffuse hepatocellular swelling ( $\sigma$ ); brown pigmentation in the liver and proximal tubules of the kidney ( $\sigma$  and  $\varphi$ ); extramedullary hematopoiesis ( $\varphi$ ) diffuse hepatocellular necrosis ( $\sigma$ ) and  $\uparrow$  auricular thrombus ( $\sigma$ ). At 100 ppm,  $\uparrow$  diffuse hepatocellular swelling and brown pigmentation in the liver were also seen in the males.

**The LOAEL is 100 ppm (10.6 mg/kg/day) based on anemia, hepatocellular swelling, necrosis and the formation of brown pigment in the liver and kidneys of male mice. This latter finding is consistent with the established mechanism of action of Oxadiazon in plants, (i.e., inhibition of porphyrin biosynthesis). The NOAEL is 10 ppm (1.09/0.92 mg/kg/day for  $\sigma/\varphi$ ).**

Discussion of Tumor Data: Neoplastic findings were: significant increases ( $p < 0.05$ - $< 0.001$ ) in liver adenomas and carcinomas in males and females at 1000 ppm; liver adenomas and carcinomas were also significantly increased at 100 ppm in males.

Adequacy of the Dose Levels Tested: Dosing was considered adequate in males and females based on anemia and pathological changes in the liver at the highest dose tested.

The pathology report for this chronic/carcinogenicity study in the mouse was considered incomplete; thus, the overall study was listed as Supplementary. At this time, additional information is not being requested because the results are consistent with an acceptable mouse carcinogenicity study (MRID No. 00115733) that satisfies the guideline requirement. Similarly, the presence of liver neoplasms confirms the evidence of a carcinogenic effect seen in other mouse long-term studies (MRID No. 00044322 and 00115733). Using the more recent terminology, the study is now listed as **Unacceptable/guideline** (MRID No. 40993301).

### **3.3     Classification of Carcinogenic Potential**

According to the Cancer Assessment Review Committee report, dated August 27, 1987 (HED Document No. 007798), the original peer review (September 9, 1986) placed Oxadiazon into Group B2 (probable human carcinogen) but there was a minority opinion that the agent should be placed in Group C (possible human carcinogen). Review of the weight-of-the-evidence on Oxadiazon by the Scientific Advisory Panel (dated November 20, 1987) reiterated this minority view. Consequently, the current Agency decision on the carcinogenic potential of Oxadiazon concurs with the Scientific Advisory Panel's (SAP) classification of Oxadiazon as a group C carcinogen. The updated  $Q_1^*$  has been set at  $1.4 \times 10^{-1}(\text{mg/kg/day})^{-1}$  in human equivalents. The rationale for the original classification as group B2 was based on the increased incidence of malignant or combined malignant and benign liver tumors: a) in multiple species (CD-1 mice and F344 rats of one or both sexes) and in multiple experiments (liver tumors in two mouse studies and in one rat study). The decision to reclassify Oxadiazon as a Group C carcinogen was based on the rationale that liver tumors were produced in two of the three positive studies (one mouse study and one rat study) at doses that exceeded the maximum tolerated dose (MTD). Since that time, a new chronic/oncogenicity toxicity study in rats (MRID No. 40993401) and a new carcinogenicity study in mice (MRID No. 40993301) have been submitted to the Agency. **The HIARC recommended that the  $Q_1^*$  be revisited and that the CARC reconvene to evaluate these more recent studies.**

## **4     MUTAGENICITY**

### **4.1     Summaries**

Nine acceptable mutagenicity studies were available for review; summaries of these studies with MRID numbers are presented below:

#### **GENE MUTATION**

a) *Salmonella typhimurium*/*Escherichia coli* reverse gene mutation assay. The assay was **negative** in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and *E. coli* WP2 *hcr* up to the highest dose tested (2500 µg/plate -S9; 1000 µg/plate +S9) of 99.18% Oxadiazon. The study is acceptable and satisfies the guideline requirements (870.5100/84-2) for a bacterial gene mutation assay (MRID No. 00069893).

b) *S. typhimurium* reverse gene mutation assay: The assay was **negative** in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 exposed to 97.49% Oxadiazon up to 5000 µg/plate +/-S9; cytotoxicity was seen at ≥3330 µg/plate -S9. The study is acceptable and satisfies the guideline requirements (870.5100/84-2) for a bacterial reverse mutation assay (MRID No. 41871701).

c) L5178Y TK +/- mouse lymphoma cell/mammalian activation forward mutation assay: The assay was **negative** in cells treated with Oxadiazon (95.5% a.i.) up to reproducibly cytotoxic levels in the absence of S9 activation (1000 µg/mL) and severely cytotoxic doses (≥200 µg/mL) with S9 activation. Oxadiazon was insoluble at ≥62.5 µg/mL. The study is acceptable and satisfies the guideline requirements (870.5300/84-2) for a mammalian cell gene mutation assay (MRID No. 00115726).

d) L5178Y TK +/- mouse lymphoma cell/mammalian activation forward mutation assay: The assay was **negative** in cells treated with recrystallized Oxadiazon (100% a.i.) up to cytotoxic levels (1000 µg/mL -S9; 250 µg/mL +S9). Oxadiazon was insoluble at concentrations ≥250 µg/mL. The study is acceptable and satisfies the guideline requirements (870.5300/84-2) for a mammalian cell gene mutation assay (MRID 00115729).

## CHROMOSOME ABERRATIONS

e) *In vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells: The assay was **negative** in cells treated with Oxadiazon (95.5% a.i.) up to cytotoxic concentrations (75 µg/mL -S9; 41.6 µg/mL +S9) and the limit of solubility (≥416 µg/mL). The study is acceptable and satisfies the guideline requirements (870.5373/84-2) for a mammalian cell chromosome aberration assay (MRID 00115730).

f) *In vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells: The assay was **negative** in cells treated with recrystallized Oxadiazon (100% a.i.) up to cytotoxic concentrations (200 µg/mL -S9; 500 µg/mL +S9) and the limit of solubility (667 µg/mL -S9; 200 µg/mL +S9). The study is acceptable and satisfies the guideline requirements (870.5373/84-2) for a mammalian cell chromosome aberration assay (MRID 00115728).

## OTHER MUTAGENIC MECHANISMS

### Unscheduled DNA synthesis(UDS)

g) UDS in primary rat hepatocytes assay: The test was **negative** in hepatocytes exposed to Oxadiazon (95.5% a.i.) up to cytotoxic concentrations (≥100 µg/mL) and the limit of

solubility ( $\geq 50$   $\mu\text{g/mL}$ ). The study is acceptable and satisfies the guideline requirements (870.5550/84-2) for a UDS assay (MRID No. 00115727).

h) UDS in primary rat hepatocytes assay: The test was **negative** in hepatocytes exposed to recrystallized Oxadiazon (100% a.i.) up to cytotoxic concentrations (100-500  $\mu\text{g/mL}$ ) and the limit of solubility ( $\geq 25$   $\mu\text{g/mL}$ ). The study is acceptable and satisfies the guideline requirements (870.5550/84-2) for a UDS assay (MRID No. 00115723).

#### In vitro cell transformation

I) *In vitro* cell transformation assay in Syrian hamster kidney BHK21 C13/HRC1 cells: The test was **positive both with and without S9 activation**, based on the induction of transformation frequencies (TFs)  $\geq 5$  times the solvent control value at the  $\text{LD}_{50}$ . Oxadiazon (90% a.i.) and recrystallized Oxadiazon (100 % a.i.) were tested up to cytotoxic concentrations with  $\text{LD}_{50}$  values in the absence of S9-mix of 118  $\mu\text{g/mL}$  and 200  $\mu\text{g/mL}$ , respectively. In the presence of S9-mix, the  $\text{LD}_{50}$  of Oxadiazon was 69  $\mu\text{g/mL}$ ; however, the  $\text{LD}_{50}$  for recrystallized Oxadiazon was not determined as cell viability was 78% of the solvent control at the highest dose tested (400  $\mu\text{g/mL}$ ). The transformation frequencies (the number of transformed colonies/ $10^6$  surviving cells) at the  $\text{LD}_{50}$  concentrations were 128 and 79 for cells treated with Oxadiazon in the absence and presence of S9-mix, respectively, compared to the solvent control values of 4 and 5, respectively. Recrystallized Oxadiazon induced transformation frequencies of 55 at the  $\text{LD}_{50}$  in the absence of S9-mix and 60 at the highest dose tested in the presence of S9-mix. A positive dose-response trend was generally apparent for both concentrations. This study is classified as acceptable (nonguideline) (MRID No. 00115703).

## **4.2 Conclusions**

In addition to the above two *S. typhimurium* reverse gene mutation assays (Ames test), seven Ames tests submitted by the sponsor were considered inadequate (see HED Document No. 002168). Nevertheless, results from these assays indicated that an impurity (identified as 24,865 RP) in Oxadiazon formulations was mutagenic in *S. typhimurium* strains TA98 and/or TA100 in the presence of S9 activation. Lots/batches of Oxadiazon with purity levels  $\leq 90\%$  that contained this impurity were also positive. As summarized above, the acceptable bacterial assays with  $\geq 97.49\%$  Oxadiazon were negative (MRID Nos. 00069893 and 41871701). Similarly, neither 95.5% Oxadiazon nor recrystallized Oxadiazon (100%) were mutagenic or clastogenic in cultured mammalian cells and did not cause UDS in primary rat hepatocytes. There is, however, evidence that both formulations induced neoplastic transformation in Syrian hamster kidney cells both in the presence and in the absence of S9 activation. The finding of positive cell transformation supports the evidence from mouse bioassays (MRID Nos. 00444322, 00115733 and 40993301) and the rat long-term studies (MRID Nos. 00149003/00157780 and 40993401) of liver tumor induction. Overall, the data indicate that Oxadiazon is not mutagenic but does cause neoplastic cell transformation *in vitro*.

## **5 FQPA CONSIDERATIONS**

### **5.1 Adequacy of the Data Base:**

Acceptable prenatal toxicity studies in rats and rabbits with Oxadiazon have been submitted to the Agency. An acceptable reproductive toxicity study in rats with Oxadiazon was also submitted. Hence, there are no data gaps for the assessment of the effects of Oxadiazon following *in utero* exposure or the effects on young animals following early exposure.

Neither acute nor subchronic neurotoxicity studies were submitted to the Agency. It is not, however, expected that Oxadiazon is a neurotoxicant since none of the acute, subchronic, chronic, developmental or reproductive toxicity studies showed evidence of an effect on the nervous system.

### **5.2 Neurotoxicity:**

No neurotoxicity studies were submitted to the Agency.

### **5.3 Developmental Toxicity**

a. Developmental Toxicity Study in the Rat (**ORAL**)                      Guideline #: 870.3700; 83-3

MRID No.: 40470202

Executive Summary: In a developmental toxicity study (MRID 40470202), Oxadiazon technical (96.3%) was administered daily by gavage in 10 ml 1% aqueous methylcellulose vehicle/kg body weight from Gestation Days 6 through 15 to groups of 20 pregnant Sprague-Dawley rats per dose at 0, 3, 12 or 40 mg/kg/day. Pregnant females were examined daily for signs of toxicity and body weights were measured on Gestation Days 0, 3, 6, daily through Day 16 and on Days 18 and 20. Dams were sacrificed on Day 20 and uterine contents were examined.

Very little maternal toxicity was observed at any dose. Small but statistically significant decreases in body weight (-2% less than controls) and body weight gain (-10%) in the high-dose females at Days 16-20 were possibly due to resorptions of fetuses (decreased maternal body weights also observed at  $\geq 40$  mg/kg/day in the range-finding study). **The maternal toxicity LOAEL is 40 mg/kg/day, based on slightly decreased body weight/weight gain. The maternal toxicity NOAEL is 12 mg/kg/day.**

Treatment-related fetal toxicity at 40 mg/kg/day included: slightly, not statistically significantly increased fetal resorptions (0.7/dam vs. 0.4/dam, controls) and post-implantation loss (12.5% vs. 8.2%, controls) and significantly decreased body weight (-4.5% less than controls). Developmental effects at 40 mg/kg/day were confined to increased incidence of incomplete ossification, primarily in skull and vertebral bones. No effects were seen at lower doses. No treatment-related malformations were observed at the doses tested. Fetal effects seen in this study are considered treatment-related based on the steep dose-response curve (for fetal loss and decreased fetal weight) between 20-60 mg/kg/day in the preliminary range-finding study. In the range-finding study, which tested at 10, 20, 40, 60 or 80 mg/kg/day (6 dams/dose group), no maternal or developmental toxicity was observed at 10 or 20 mg/kg/day. However, at 40 mg/kg/day, a mean fetal resorption rate of 40% (53-100% in 3/6 dams) was observed, increasing to 80-90% at 60 and 80 mg/kg/day. Weights of surviving fetuses were decreased. Decreased maternal weights were also observed at  $\geq 40$  mg/kg/day and were usually correlated with the increased litter resorption. Therefore, the effects seen at 40 mg/kg/day **in the main study** are considered a threshold response for Oxadiazon under the conditions of the main study. **The developmental toxicity LOAEL (threshold) is 40 mg/kg/day, based on increased fetal resorptions/postimplantation loss, decreased fetal weight and increased incidence of incomplete ossification. The developmental toxicity NOAEL (threshold) is 12 mg/kg/day.**

This study is classified **Acceptable/guideline**; it satisfies the guideline requirement for a developmental toxicity study (83-3a) in the rat.

b. Developmental Toxicity Study in the Rabbit (**ORAL**) Guideline #: 870.3700; 83-3

MRID No.: 40470201

Executive Summary: In a developmental toxicity study (MRID 40470201), Oxadiazon technical (95.6%) was administered daily by gavage in 5 ml 1% aqueous methylcellulose vehicle/kg body weight from gestation days 6 through 19 to groups of 15 to 19 pregnant New

Zealand White rabbits per dose at 0, 20, 60 or 180 mg/kg/day. Pregnant females were examined daily for signs of toxicity and body weights were measured on Gestation Days 0 and 6, on alternate days through day 20 and on days 24 and 28. Dams were sacrificed on Day 29 and uterine contents were examined.

Treatment-related maternal toxicity was observed at 60 mg/kg/day as transient weight loss (-0.01 kg vs. 0.10 kg gain, controls;  $p < 0.05$ ) and slightly decreased food consumption during the first half of treatment (-15% less than controls, treatment days 6-12; not statistically significant). These effects were more pronounced at 180 mg/kg/day and showed statistically significant reductions in weight gain and marked reductions in food consumption during and after treatment. **The maternal toxicity LOAEL is 60 mg/kg/day, based on transient weight loss and decreased food consumption during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.**

Treatment-related fetal toxicity at 180 mg/kg/day included: increased postimplantation loss and late resorptions (18.85% vs. 8.6%, controls;  $p < 0.05$ ), decreased mean fetal weight (-10%) and increased incidence of bilateral hind-limb flexure (4.2% of fetuses, 3 litters affected vs. 0%, controls). Marginal developmental effects at 180 mg/kg/day were: increased incidence of rib abnormalities, delayed/incomplete ossification in several bones and asymmetrical pelvis. No effects were seen at lower doses and there were no treatment-related malformations observed at any dose tested. **The developmental toxicity LOAEL is 180 mg/kg/day, based on increased postimplantation loss, decreased mean fetal weight, increased bilateral hind-limb flexure and possibly delayed/incomplete ossification of several bones. The developmental toxicity NOAEL is 60 mg/kg/day.**

This study is classified **Acceptable/guideline**; it satisfies the guideline requirement for a non-rodent developmental toxicity study (83-3b) in the rabbit.

#### **5.4 Reproductive Toxicity**

Two Generation Reproduction Study in Rats (dietary)      Guideline #: 870.3800; 83-4a

MRID Nos. 41230301(Dose-range finding study)/ 41239801 (Main study)

Executive Summary: In a 2-generation reproduction study (MRID 41239801; range-finding study MRID 41240301) Oxadiazon (96.6% a.i., batch # DA459) was administered in the diet continuously to CD rats (30 rats/sex/dose) at 0, 20, 60 or 200 ppm (equivalent to an average daily intake [M/F] of 0, 1.50/1.84, 4.65/5.63 or 15.50/18.20 mg/kg/day, average of P and F<sub>1</sub> generation pre-mating food consumption). Dose levels were selected based on the results of the 1-generation range-finding study, which tested at 0, 50, 100, 200, 400 or 800 ppm (6 animals/sex/dose, 4 weeks pre-mating exposure). The P animals were exposed to the test substance beginning at approximately 6 weeks of age for 14 weeks prior to mating and continuing until sacrifice after weaning (post-partum day 25). F<sub>1</sub> pups selected (30/sex/dose) to produce the F<sub>2</sub> generation were exposed to the same dosage as their parents beginning at postnatal day (PND) 25 for 14 weeks pre-mating and continuously throughout the rest of the

study until weaning of the F<sub>2</sub> offspring (postpartum day 25). Liver, kidneys, ovaries, uterus, prostate, epididymis, testes and seminal vesicles were weighed and examined for gross/microscopic pathology. Mammary gland, pituitary and vagina were examined for pathological changes. The 1-generation range-finding study tested in 6 dams/dose group at dietary concentrations of 0, 50, 100, 200, 400 or 800 ppm (0, 5/5, 9/9, 19/19, 36/38 or 67/75 mg/kg/day, respectively), administered beginning 15 days prior to initiation of mating until lactation day 4. No treatment-related findings were reported at  $\geq 200$  ppm; effects at 400 and 800 ppm are discussed below.

There was no evidence of treatment-related changes in clinical signs, mortality, body weights or weight gains, food consumption, food efficiency, organ weights or microscopic or macroscopic pathology observed in P or F<sub>1</sub> adults in the main study. Slight liver alterations in F<sub>1</sub> adults at 200 ppm (+6% relative liver weight, females, periportal hepatocellular hypertrophy, males) were considered an adaptive response. However, at 400 ppm in the range-finding study, markedly decreased gestational weight gain (-34% below controls, primarily after GD 13) was observed (due largely to increased fetal loss). At 800 ppm, decreased maternal weight gain of -38% below controls, also primarily after GD 13, blood in the urine in the cage paper of males and blood in the nares/face/urogenital region of 1 dam were observed. **The LOAEL (main study) for parental toxicity is  $>200$  ppm (15.5 mg/kg/day; HDT in main study); however, a LOAEL of 400 ppm (38 mg/kg/day), based on decreased gestational weight gain, was observed in the range-finding study. The parental toxicity NOAEL (main study) is  $\geq 200$  ppm.**

No differences in reproductive parameters in P or F<sub>1</sub> parental animals, nor in F<sub>1</sub> or F<sub>2</sub> offspring viability, clinical signs, body weight or body weight gain, developmental landmarks, auditory or ophthalmological function or macroscopic pathology were observed in the main study. However, in the range-finding study, pronounced reproductive/offspring toxicity at 400 ppm in the 4 dams that littered (5 pregnant) included inactive/pale mammary tissue, reduced litter size and increased gestation length (+1 day). Pre-/perinatal mortality resulted in total litter losses for all dams by day 1 postpartum (17 offspring were examined: 20% late resorptions, 7.7% dead fetus, 73% without milk in stomach). At 800 ppm, 2 dams littered but all were late resorptions; 4 dams that failed to litter had blood in their cage on GD 23 (implantation sites/dam were comparable to controls). **The reproductive/offspring toxicity LOAEL (main study) is  $>200$  ppm (15.5 mg/kg/day; HDT in main study); however, a LOAEL of 400 ppm (38 mg/kg/day), based on inactive mammary tissue and fetal/neonatal death, was observed in the range-finding study. The reproductive/offspring toxicity NOAEL (main study) is  $\geq 200$  ppm.**

This reproductive toxicity study in the rat is classified **Acceptable/guideline** [§83-4(a)] and satisfies the guideline requirement for a multigenerational reproductive toxicity study in rats. Although no significant effects were observed at  $\geq 200$  ppm in the main or range-finding studies, pronounced reproductive/offspring toxicity, including complete litter loss, was observed at  $\geq 400$  ppm. **The HIARC concluded that the neonatal loss seen at 400 ppm was attributable to maternal effects (*i.e.*, inactive mammary tissue resulting in possible starvation of the pups which was manifested as 73% of the examined offspring**

without milk in their stomachs). The HIARC further concluded that the inactivity of mammary tissue may have been related to endocrine disruption. However, this finding was not considered to be likely because there was no supporting evidence of possible endocrine disruption observed in any other study in the Oxadiazon database.

### **5.5 Additional Information from Literature Sources (if available)**

No additional information was obtained from the open literature for developmental, reproductive or neurotoxic effects of Oxadiazon.

### **5.2 Determination of Susceptibility**

There was qualitative evidence of increase susceptibility of fetuses in the rat developmental study. In this study, very little maternal toxicity (a small but significant decrease in body weight, -2% and a decrease in body weight gain, -10%) was seen at the maternal and developmental LOAEL (40 mg/kg/day). By contrast, effects on offspring at this LOAEL were severe (increased post-implantation loss and late resorptions and decreased fetal weight). In the two generation study in rats, neonatal effects (LOAEL of 38 mg/kg/day, based on neonatal losses) in the dose range-finding phase of testing and the lack of milk in the pup stomach were considered to be attributable to maternal effects (i.e., inactive mammary tissue) at 38 mg/kg/day. The findings of post-implantation loss associated with the lack of milk could be due to endocrine disruption. There was, however, no evidence (qualitative or quantitative) of increased susceptibility in the developmental rabbit study following *in utero* exposure or in the two-generation reproduction study following pre- or post-natal exposure.

### **5.3 Recommendation for a Developmental Neurotoxicity Study**

The Committee concluded that a developmental neurotoxicity study was **not recommended**. This decision was based on results showing no evidence of neurotoxicity in any study in the database which included: chronic (rats, mice and dogs), subchronic (rat or rabbit), reproduction (rat) or developmental (rat or rabbit) toxicity studies.

## **6 HAZARD CHARACTERIZATION**

Oxadiazon is a selective pre-emergent herbicide of the oxadiazole class which displays light-dependent phytotoxicity through the accumulation of protoporphyrin IX in plants, yeast and mouse liver mitochondria. At present, there are no registered food or residential uses. The database for Oxadiazon is largely complete and provides sufficient information to characterize toxicity. The only data gap that has been identified at this time is the submission of a 28- and/or 90-day inhalation study.

In acute studies, Oxadiazon is only slightly toxic (Toxicity Categories III or IV) with an oral LD<sub>50</sub> >5000 mg/kg, a dermal LD<sub>50</sub> >2000 mg/kg and an inhalation LC<sub>50</sub> > 1.94 mg/L.

Oxadiazon is mildly irritating to ocular tissue and negligibly irritating to the skin (both Toxicity Category III) and is not a dermal sensitizer.

The major target organ of Oxadiazon is the liver. Effects were consistent among the species tested (rat, dog, mouse) in both subchronic and chronic studies and typically included enlarged livers (presumably due to the peroxisomal proliferating activity of Oxadiazon), along with increases in serum clinical chemistry parameters associated with hepatotoxicity such as alkaline phosphatase and serum aspartate or alanine aminotransferase. Although treatment-related microscopic lesions of the liver were not observed in dog subchronic or chronic oral studies, findings in rats and mice included pigmented Kupffer cells and bile canaliculi, periportal pallor, increased acidophilic cells and hepatocellular necrosis. The hematopoietic system also appeared to be a target of Oxadiazon in all three species, based on mild anemia (reductions in RBC, hematocrit and/or hemoglobin). Increased pigmentation in the kidney was observed in rats, along with increased BUN and kidney weights. Although a dose-dependent increase in thyroid weight was observed in the dog subchronic oral toxicity study, treatment-related changes in thyroid weights or gross/microscopic observations were not observed in other studies (thyroid hormones were not evaluated).

In a rat dermal absorption study, up to  $\approx 9\%$  of the applied dose was absorbed after 10 hours of exposure. Dermal toxicity studies (21-day rabbit) support low dermal absorption: no toxicity was observed at the limit dose of 1000 mg/kg/day.

Following long-term dietary administration, Oxadiazon caused an increased incidence of hepatocellular adenoma and carcinoma in rats and mice. In mice, statistically significant increases of hepatocellular adenoma and combined adenoma/adenocarcinoma were observed at all four dose levels tested ( $\geq 100$  ppm) in males and females. The incidence of hepatocellular adenocarcinoma was increased at all doses in males but only at the two highest doses (1000 and 2000 ppm; significant at 1000 ppm) in females. The highest dose tested in males (2000 ppm) exceeded the MTD based on excessive mortality. In SPF Wistar rats, the incidence of hepatocellular adenomas was increased in males; adenocarcinomas were increased but not significantly in both sexes at the highest dose tested (1000 ppm). A second study in F344 rats showed an increased incidence of hepatocellular adenoma and adenocarcinoma only in males at 1000 and 3000 ppm. A classification of Group C (possible human carcinogen) and a  $Q_1^*$  of  $1.4 \times 10^{-1}$  (mg/kg/day) $^{-1}$  were assigned by the HED Cancer Peer Review Committee in conjunction with the recommendations of the Scientific Advisory Panel. Since that time, a new chronic/oncogenicity toxicity study in rats and a new carcinogenicity study in mice have been submitted to the Agency and are being evaluated for their impact on the cancer classification and the  $Q_1^*$ .

In a special mechanistic study in rats, Oxadiazon induced peroxisomal proliferation (based on peroxisomal enzyme induction and electron microscopy) after a 14-day dietary administration. Although some peroxisomal proliferator compounds are known to be liver carcinogens, there are insufficient data available to support this as a mechanism of carcinogenicity for Oxadiazon. Similarly, Oxadiazon did not show mutagenic potential in any *in vitro* assays with bacteria (*S. typhimurium* and *E. coli*) or mammalian cells (TK +/-mouse lymphoma

cells), did not show clastogenic potential in the *in vitro* Chinese hamster ovary cell chromosomal aberration assays and did not induce unscheduled DNA synthesis in cultured primary rat hepatocytes. However, a dose-related increase in transformation frequencies was observed in an *in vitro* Syrian hamster kidney BHK21 C13/HRC1 cell transformation assay.

Significant fetal toxicity (fetal loss due to resorptions and post-implantation loss, decreased fetal weight, skeletal variations) was observed in developmental toxicity studies in both rats and rabbits and in a rat two-generation reproduction study. Neonatal survival was also sharply reduced in the reproduction study. The latter finding was due at least in part to effects on lactation, based on findings of inactive mammary glands in the dams at necropsy. These fetal/neonatal effects occurred at the same dose levels at which maternal toxicity (decreased weight gain/weight loss) were observed. It is likely that neonatal loss may have resulted from starvation and would, therefore, be an effect of direct maternal toxicity. Inactivity of the mammary tissue as a possible effect of endocrine disruption was considered but was not found to be likely since there was no evidence from any other study in the database suggesting endocrine disruption. No fetal malformations were observed in the rat or rabbit developmental toxicity studies although, some skeletal variations (delayed ossification, asymmetric pelvis) were reported. There was, however, no evidence (qualitative or quantitative) of increased susceptibility in the developmental rabbit study following *in utero* exposure or in the two-generation reproduction study following pre- or post-natal exposure.

No neurotoxicity studies have been submitted for Oxadiazon. However, the available data do not indicate a need for neurotoxicological testing. No clinical signs of toxicity suggestive of neurobehavioral alterations nor evidence of neuropathological effects were observed in the available oral toxicity studies. There was no evidence for neurodevelopmental potential of Oxadiazon in the rat and rabbit developmental toxicity studies, nor in the rat two-generation reproductive toxicity study.

Based on pharmacokinetics/metabolism studies in the rat, low doses (5 mg/kg, single or multiple) of Oxadiazon were completely absorbed, metabolized and excreted in the urine and feces; virtually no free Oxadiazon was found in the urine. At this dose, the rates and routes of excretion of radioactivity were similar. At 500 mg/kg, the rate of excretion was affected but the route was not. The excretion of radioactivity into the urine and the feces was sex dependent and the tissue residues were very low in all tissues except liver and fat. Over a 7-day period, 85 to 93% of the test compound administered was excreted in the urine and feces. The radioactivity recovered in the urine, feces and tissues exceeded 94% of the dose and was sex-related. Females excreted more radioactivity in the urine than males. The metabolism of Oxadiazon in rats was extensive, but the benzene and pyrazolidine rings were not modified. Eighteen (18) metabolites were identified in the urine and feces. Four (4) urinary and 5 fecal metabolites were present at levels greater than 1% of the dose. Among the 9 metabolites, U2, U7 and U10 from the urine correspond to F2, F7 and F9 of the feces. Female rats were efficient metabolizers and the urine was unique in that metabolites U4 and U5 were excreted in the urine only. Only conjugates of glucuronic acid were present in urine; there was no evidence of sulphate conjugates. The identified glucuronides were those of metabolites RP 29585 and RP25496. In addition to 5 fecal metabolites, intact Oxadiazon was present in feces

only and was dose-related. At the high dose more than 53% of the administered radioactivity was intact Oxadiazon in the feces; at 5 mg/kg, not more than 4.8% of the dose was intact Oxadiazon in the feces. This observation is consistent with extensive absorption followed by excretion in the feces by way of the bile.

## 7 DATA GAPS

HIARC **has requested** the submission of a 28-day inhalation study.

## 8 ACUTE TOXICITY

### Acute Toxicity of Oxadiazon

| Guideline No.       | Study Type  | MRIDs #  | Results   | Toxicity Category |
|---------------------|---|----------|---|-------------------|
| 870.1100/<br>[81-1] | Acute Oral; Rat<br>97.5 % a.i.                    | 41866501 | LD <sub>50</sub> = > 5000 mg/kg<br>(♂♀, combined) | IV                |
| 870.1200/<br>81-2   | Acute Dermal; Rabbit<br>97.5 % a.i.               | 41866502 | LD <sub>50</sub> = > 2000 mg/kg<br>(♂♀, combined) | III               |
| 870.1300/<br>81-3   | Acute Inhalation; Rat<br>93.7 % a.i.              | 41866503 | LC <sub>50</sub> = > 1.94 mg/L<br>(♂♀, combined)  | III               |
| 870.2400/<br>81-4   | Primary Eye Irritation;<br>Rabbit<br>97.5 % a.i.  | 41866504 | Mild irritant to ocular<br>tissue                 | III               |
| 870.2500/<br>81-5   | Primary Skin Irritation;<br>Rabbit<br>97.5 % a.i. | 41866505 | Negligibly irritating to<br>skin                  | III               |
| 870.2600/<br>81-6   | Dermal Sensitization;<br>Guinea pig<br>93.7% a.i. | 41230401 | Not a dermal sensitizer<br>(Buehler test)         | --                |
| 81-8                | Acute Neurotoxicity                               | ND       |   |                   |

## 9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

| EXPOSURE SCENARIO                             | DOSE (mg/kg/day)   | ENDPOINT  | STUDY  |
|---|--|---|--|
| Acute Dietary                                 | NOAEL= N/A<br>UF = N/A   |   |  |
|   | <b>This risk assessment is not required because there are no food or feed uses for Oxadiazon</b> |   |  |
| Chronic Dietary                               | NOAEL = N/A<br>UF = N/A  |   |  |
|   | <b>This risk assessment is not required because there are no food or feed uses for Oxadiazon</b> |   |  |
| Cancer  | $Q_1^*$ of $1.4 \times 10^{-1}$ (mg/kg/day) <sup>-1</sup> in human equivalents <sup>a</sup>      | Group C “possible human carcinogen”, based on liver tumors produced in two of the three positive studies (one mouse study and one rat study) at doses that exceeded the maximum tolerated dose. | Combined Chronic Toxicity/ Carcinogenicity Study in Rats<br>MRID Nos. 00149003/ 00157780;<br>Carcinogenicity Study in Mice<br>MRID Nos. 00115733 |
| Incidental Oral, Short- and Intermediate-Term | NOAEL= 12  | Reduced body weight/body weight gain at 40 mg/kg/day (LOAEL).   | Developmental Toxicity -Rat<br>MRID No. 40470202   |
| Dermal, Short- and Intermediate-Term          | NOAEL= 12  | Increased fetal resorptions/ postimplantation loss, decreased fetal weight and increased incidence of incomplete ossification at 40 mg/kg/day (LOAEL) <sup>b</sup> .                            | Developmental Toxicity -Rat<br>MRID No. 40470202   |

| EXPOSURE                      | DOSE<br>(mg/kg/day) | ENDPOINT  | STUDY  |
|-------------------------------|---------------------|---|--|
| Dermal, Long-Term             | NOAEL= 0.36         | Increased centrilobular swelling in male livers at 3.5 mg/kg/day (LOAEL) <sup>b</sup> . | Combined Chronic Feeding/<br>Oncogenicity - Rat<br>MRID Nos.<br>40993401,<br>00149003/<br>00157780 |
| Inhalation, Short-Term        | NOAEL= 12           | Reduced body weight/body weight gain at 40 mg/kg/day (LOAEL) <sup>c</sup> .             | Developmental Toxicity - Rat<br>MRID No.<br>40470202   |
| Inhalation, Intermediate-Term | NOAEL= 12           | Reduced body weight/body weight gain at 40 mg/kg/day (LOAEL) <sup>c</sup> .             | Developmental Toxicity - Rat<br>MRID No.<br>40470202   |
| Inhalation, Long-Term         | NOAEL= 0.36         | Increased centrilobular swelling in male livers at 3.5 mg/kg/day (LOAEL) <sup>c</sup> . | Combined Chronic Feeding/<br>Oncogenicity - Rat<br>MRID Nos.<br>40993401,<br>00149003/<br>00157780 |

<sup>a</sup> Q<sub>1</sub>\* may change awaiting the outcome of the CARC revisit.

<sup>b</sup> For this risk assessment, the dermal absorption factor of 9% should be applied.

<sup>c</sup> For this risk assessment, use a route-to-route extrapolation and a 100% absorption rate (default value).